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Formulation and Evaluation of Antimalarial Drugs of Nano Lipid based drug delivery system

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ABSTRACT
This paper is about formulation and evaluation of nano lipid based antimalarial drugs Artemether and lumefantrine by forming liposomes by the means of parentral route. Liposomes were chosen as they provide continuous medication release, which lowers dosage frequency and improves patient compliance. Additionally, these nanoliposomes could direct medication to the liver, which is where it acts. Parentral route is used since it will solve the bioavailability issue with oral and intramuscular routes. This approach will further result in dose and dose frequency reduction, resulting in therapeutic patient compliance.

I. INTRODUCTION

There are four main Plasmodium species that cause human malaria, including P. vivax, P. falciparum, P. malariae, and P. ovale. The main causes of the subpar clinical effectiveness of anti-malarial medications include the poor and variable oral bioavailability, a lack of dose proportionality, & gastrointestinal tract degradation. Malaria treatment is hampered by two key factors: rapid medication resistance & extensive occurrence. It takes a lot of time and money to discover novel chemical entities & develop commercially viable formulations.

The herb Artemisia annua (Compositae), which has a unique sesquiterpene lactone with a peroxy group, is used to make the potent antimalarial medication artemether. It is triggered by intra-parasitic heme iron, which catalyses the cleavage of endoperoxide inside malaria parasites. It has excellent antimalarial activity and low toxicity because of its distinct structure and mode of action.

It is feasible to trap both hydrophilic and/or hydrophobic drugs there simultaneously and effectively thanks to the phospholipid bilayer membrane structure of liposomes. Using liposomes can improve drug distribution in living things while reducing drug release in vivo. The medicine's plasma concentration-time profile in nanoliposomes demonstrated a larger enhancement in the drug's bioavailability. Due to all of their beneficial characteristics, nanoliposomes are a better method of transport for artemether and lumefantrine.

The two main components of liposomes, which are self-assembling lipid bilayers with an aqueous centre, are cholesterol and amphiphilic phospholipids. Hydrophobic and hydrophilic substances can be enclosed in a bilayer or an inner cavity using a variety of loading techniques. To improve target selectivity and reduce enzymatic drug degradation, certain ligands can be converted into liposomal carriers. Numerous liposomal medications can be used to treat various cancer types.

II. METHODOLOGY

Preparation of Vesicle

Liposomes were produced under carefully regulated conditions using the ether injection technique.

- Soy lecithin and cholesterol were first dissolved in 20 cc of ether at various concentrations. Drugs were either dissolved separately or in combination in chloroform.
- The 25 cc of the aqueous phase containing pluronic F68 was then gently mixed with the organic phase. The solution was heated to 60 °C and stirred magnetically to evaporate the organic phase.
- The remaining portions of the organic phase were then extracted using a rotary evaporator working at a reduced pressure. The size of the resulting dispersion was further diminished using an ultrasonicator.
- Sucrose was used to prevent the nanoliposomes from freezing before they were freeze dried.
- By rehydrating lyophilized nanoliposomes with distilled water to make an aqueous

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solution, it was required to check whether sucrose was effective as a cryoprotectant at the concentration utilised.

- All formulations were stored at 5 °C before to use. Lumefantrine and artemether were formulated in a variety of concentrations, both separately and jointly, to optimise the final product.

III. RESULT AND DISCUSSION

Stability studies for nanoliposomes

The particle size of the NLs rose steadily over course of 60 days, from 120.6 to 150.1 nm. The partial aggregation caused by reduction in high surface-to-volume ratios may have had a role in 24 percent increase in particle size seen in NLs after 60 days. However, only a 27% increase in particle size was seen after 60 days when NLs were freeze dried.

S. No	Time (Days)					
	0	**10**	**15**	**30**	**45**	**60**
Nanoliposomes before drying						
Vesicle Size (nm)	120.6 ± 9.4	121.3 ± 7.2	126.5 ± 8.4	135.8 ± 8.2	142.4 ± 6.6	150.1 ± 7.8
PDI	0.25	0.26	0.28	0.30	0.36	0.38
EE-ART (%)	61.2 ± 3.5	60.3 ± 5.2	60.6 ± 2.6	59.5 ± 6.4	56.5 ± 4.3	55.9 ± 3.7
EE-LMF (%)	47.3 ± 2.7	47.3 ± 2.9	45.1 ± 2.2	43.8 ± 3.6	42.5 ± 3.7	40.3 ± 2.9
Nanoliposomes after drying						
Vesicle Size (nm)	125.3 ± 10.2	128.6 ± 8.2	132.3 ± 8.2	145.8 ± 9.3	151.9 ± 8.2	158.7 ± 10.3
PDI	0.23	0.24	0.33	0.36	0.37	0.38
EE-ART (%)	66.2 ± 2.8	65.2 ± 2.2	65.2 ± 3.5	64.4 ± 3.6	62.2 ± 3.2	60.7 ± 3.2
EE-LMF (%)	53.5 ± 2.4	53.1 ± 2.7	52.2 ± 2.8	51.8 ± 3.4	51.7 ± 3.3	49.2 ± 3.2

Results of accuracy and precision

Stock solutions with an ART concentration of 5 g/mL and a LUM concentration of 30 g/mL were used to show the precision and accuracy of the method. The experiment was carried out three times with six replicate dilutions of the same concentration every two hours on the same day in order to analyse intraday precision and accuracy. Three separate days were used to evaluate the accuracy and precision between days. While accuracy was evaluated using the (drug identified / drug present) percentage recovery multiplied by 100

Drug Present	Parameter	Intra-day	Inter-day
Artemether 5 µg/mL	Drug found	4.98	5.06
	Precision as CV %	5.9	5.3
	Accuracy (%)	99.88	101.6

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Lumefantrine 30 µg/ml	Drug found	30.13	30.07
	Precision as CV %	1.5	1.3
	Accuracy (%)	100.41	100.26

Pharmacokinetic data of ART-LUM solution and nanoliposome formulation

The ART+LUM-NLs solution had a substantially higher AUC than the ART+LUM solution. Although the drug's initial concentration in plasma was higher than it was in ART+LUM solution (Cmax), PK data demonstrate that drug was swiftly flushed from circulatory systemEven though ART+LUM-NLs contained less medication than ART+LUM solution, they displayed a longer MRT, or prolonged residence period of ART+LUM in systemic blood circulation.The results suggested that ART+LUM-NLs would be effective at low doses. According to these results, the parenteral liposomal formulation of lumefantrine and artemether would be adequate to address the problem of drug resistance while simultaneously enhancing efficacy and minimising side effects.

PK Parameter	**Solution**		**Nanoliposomes**	
	Artemether	**Lumefantrine**	**Artemether**	**Lumefantrine**
C_{max} (ng/ml)	2938.0 ± 362.5	2540.0 ± 227.9	2097.7 ± 374.4	1825.0 ± 325.7
AUC_{0-t} (ng.h/ml)	6352.4 ± 123.2	4319.5 ± 212.3	20750.5 ± 1453.6	11552.6 ±1251.4
$AUC_{0-\infty}$ (ng.h/ml)	6583.3 ± 136.3	4598.0 ± 111.6	20962.6 ± 1142.4	11864.4 ± 1264.3
MRT (h)	4.33 ± 0.32	3.87 ±0.42	13.86 ± 0.86	12.46 ± 0.45
V_d (L/kg)	2.28 ± 0.32	2.22 ± 0.16	2.58 ± 0.54	2.39 ± 0.56
CL (L/h/kg)	1.35 ± 0.83	1.33 ± 0.22	0.64 ± 0.12	0.54 ± 0.42
t1/2 (h)	9.63 ± 5.73	8.78 ± 5.73	12.53 ± 3.12	11.42 ± 5.73

IV. CONCLUSION

ART+LUM-NLs demonstrated that liver (40.4 percent) and spleen (26.2 percent) exhibited considerable drug concentrations, in contrast to ART+LUM solution. Schizontocyte treatment is primarily used in liver and spleen, therefore results speak for themselves.

The improved biodistribution of drugs in the liver and spleen as a result of the developed liposomal formulation further demonstrates the effectiveness of the system. Furthermore, compared to solution, liposomal formulation showed that modest medicine concentrations were found in the kidney, lung, and heart. The liposomal formulation is significantly less dangerous than the solution formulation, based on the biodistribution pattern.

Following the aforementioned conclusions, toxicological, pharmacokinetic, and biodistribution studies showed that nanoliposomes successfully created using the ether injection approach and co-loaded with lumefantrine and artemether displayed improved safety and efficacy characteristics. Therefore, developing a liposomal formulation of artemether and lumefantrine for

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parenteral administration is a novel strategy for treating malaria in an emergency.

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